

**In the Claims:**

1. (Withdrawn) A composition used for diagnosing a lysosomal storage disorder (“LSD”) comprising:  
  
a capture antibody conjugated to a microsphere; and  
  
the microsphere having at least a first fluorophore and a second fluorophore wherein,  
  
the capture antibody is capable of binding a target antigen and the target antigen comprises an LSD associated biomolecule.
2. (Withdrawn) The composition of claim 1, further comprising a detection antibody, wherein the detection antibody is capable of binding the target antigen, but is different from the capture antibody; and the detection antibody is conjugated to a detection label.
3. (Withdrawn) The composition of claim 1, wherein the target antigen is  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, saposin C, LAMP-1, or LAMP-2.
4. (Withdrawn) The composition of claim 1, wherein the target antigen is  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, iduronate-2-sulphatase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-activator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein

thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

5. (Withdrawn) The composition of claim 1, wherein the first fluorophore is spectrally distinct from the second fluorophore.
6. (Withdrawn) The composition of claim 1, wherein the microsphere has a diameter of about 5  $\mu\text{m}$ .
7. (Withdrawn) The composition of claim 1, wherein the LSD is Fabry; Mucopolysaccharidosis type I ("MPS I"); Mucopolysaccharidosis type II ("MPS-II"); Mucopolysaccharidosis type III ("MPS-III"); Mucopolysaccharidosis type IV ("MPS-IV"); or Glycogen storage disease II ("Pompe").
8. (Withdrawn) The composition of claim 1, wherein the LSD is Gaucher disease types I / II / III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB; Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IIID; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis;  $\beta$ -Mannosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ - Mannosidosis; Mucolipidosis type I; Mucolipidosis types II / III; Mucolipidosis type IIIC; Mucolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid

Lipofuscinosis, CLN3; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pycnodysostosis; or Sialic acid storage disease.

9. (Withdrawn) A protein profiling method for diagnosing a pre-clinical status, or a clinical status, of a lysosomal storage disorder (“LSD”) in a target animal comprising:
- a) determining at least a first target biomolecule quantity from a target biological sample of the target animal;
  - b) determining at least a second target biomolecule quantity from the target biological sample of the target animal;
  - c) assigning an adjusted target quantity by calculating a target proportion between the first target biomolecule quantity and the second target biomolecule quantity;
  - d) obtaining a first reference biomolecule quantity of a reference biological sample from a reference animal, or group of reference animals, having a known LSD pre-clinical or clinical status;
  - e) obtaining a second reference biomolecule quantity of a reference biological sample from a reference animal, or group of reference animals, having a known LSD pre-clinical or clinical status;
  - f) assigning an adjusted reference quantity by calculating a reference proportion between the first reference biomolecule quantity and the second reference biomolecule quantity;

g) comparing a deviation of the adjusted target quantity to the adjusted reference quantity;

wherein,

the first target biomolecule is the same or equivalent to the first reference biomolecule;

the second target biomolecule is the same or equivalent to the second reference biomolecule; and

the deviation of the adjusted, target quantity from the adjusted reference quantity is a pre-clinical or clinical indication of a specific LSD.

10. (Withdrawn) The protein profiling method of claim 9, wherein the target biological sample and the reference biological sample is selected from a cellular extract, blood, plasma, or urine.

11. (Withdrawn) The protein profiling method of claim 9, wherein the first target biomolecule and the first reference biomolecule are each  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, saposin C, LAMP-1, or LAMP-2.

12. (Withdrawn) The protein profiling method of claim 9, wherein the second target biomolecule and the second reference biomolecule are each  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, saposin C, LAMP-1, or LAMP-2.

13. (Withdrawn) The protein profiling method of claim 9, wherein the first target biomolecule and the first reference biomolecule are each  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, iduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,

$\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-activator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

14. (Withdrawn) The protein profiling method of claim 9; wherein the second target biomolecule and the second reference biomolecule are each  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, iduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-activator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

15. (Withdrawn) The protein profiling method of claim 9, wherein the second target biomolecule and the second reference biomolecule are each an indicator of cell number, organelle number, cell size, organelle size, cell volume, or organelle volume.

16. (Withdrawn) The protein profiling method of claim 9, wherein the second target biomolecule and the second reference biomolecule each comprise LAMP-1, LAMP-2, saposin C, CD45 leukocyte common biomolecule, LIMP II, CD63.
17. (Withdrawn) The protein profiling method of claim 9, wherein the LSD is Fabry; Mucopolysaccharidosis type I ("MPS I"); Mucopolysaccharidosis type II ("MPS-II"); Mucopolysaccharidosis type III ("MPS-III"); Mucopolysaccharidosis type IV ("MPS-IV"); or Glycogen storage disease II ("Pompe").
18. (Withdrawn) The protein profiling method of claim 9, wherein the LSD is Gaucher disease types I / II / III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB; Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IIID; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis; Fucosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ -Mannosidosis; Mucolipidosis type I; Mucolipidosis types II / III; Mucolipidosis type IIIC; Mucolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1 ; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid Lipofuscinosis, CLN3 ; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pycnodysostosis; or Sialic acid storage disease.

19. (Withdrawn) The protein profiling method of claim 9, further comprising confirming the pre-clinical, or clinical, status the LSD in the target animal using a substrate protein profiling method or select activity assay method.
20. (Withdrawn) The protein profiling method of claim 19, wherein the substrate protein profiling method comprises an LSD oligosaccharide determination and the select activity assay comprises an immuno-capture assay.
21. (Withdrawn) The protein profiling method of claim 9, wherein administering, monitoring, or modifying an LSD therapy in the subject is determined by comparing:
- a) the deviation of the adjusted target quantity to the adjusted reference quantity in the target biological sample; and
  - b) a second deviation of a second adjusted target quantity to a second adjusted reference quantity in a second target biological sample;
- wherein the second target biological sample is obtained at a different time point than the target biological sample and a magnitude of divergence between the deviation and the second deviation determines whether the LSD therapy will be administered, monitored, or modified.
22. (Withdrawn) A protein profiling method for determining an amount of at least a first target antigen and at least a second target antigen indicative of lysosomal storage disorder (“LSD”) in a target biological sample, the protein profiling method comprising:
- a) incubating at least a first capture antibody microsphere and at least a second capture antibody microsphere with the target biological sample forming a capture suspension;

- b) recovering the first capture antibody microsphere and the second capture antibody microsphere from the capture suspension forming a first recovered microsphere and a second recovered microsphere;
  - c) hybridizing the first recovered microsphere and the second recovered microsphere with at least first a first detection antibody and at least a second detection antibody, respectively, forming a detection suspension;
  - d) recovering the first recovered antibody microsphere and the second recovered antibody microsphere from the detection suspension forming a first detected microsphere and a second detected microsphere;
  - e) passing the first detected microsphere and second detected microsphere through an examination zone;
  - f) determining a first quantity of the first detection antibody associated with the first detected microsphere, and a second quantity of the second detection antibody associated with the second detected microsphere by (i) collecting data relating to one or more microsphere classification parameters, (ii) collecting data relating to the presence or absence of the first- or second- detection antibody on the first- or second- recovered microsphere; and (iii) quantifying the amount of first- or second- detection antibody on the first- or second- recovered microsphere;
- wherein,



the first capture antibody microsphere comprises a first capture antibody conjugated to a first microsphere, and the second capture antibody microsphere comprises a second capture antibody conjugated to a second microsphere;

the first microsphere is spectrally distinct from the second microsphere;

the first capture antibody and the first detection antibody are distinct, but each binds a first LSD associated target antigen;

the second capture antibody and the second detection antibody are distinct, but each binds a second LSD associated target antigen;

the first target antigen and second target antigen are different;

the first detection antibody is conjugated to a first fluorescent detection label;

the second detection antibody is conjugated to the first fluorescent detection label or a second fluorescent detection label;

the quantity of the first- or second- detection antibody is proportional to the amount the first- or second- target antigen in the target biological sample.

23. (Withdrawn) The protein profiling method of claim 22, wherein the target biological sample is selected from a cellular extract, blood, plasma, or urine.

24. (Withdrawn) The protein profiling method of claim 22, wherein the first target antigen is  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, or saposin C.

25. (Withdrawn) The protein profiling method of claim 22, wherein the second target antigen is  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, or saposin C.

26. (Withdrawn) The protein profiling method of claim 22, wherein the first target antigen is  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, Iduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine-N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-actvator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

27. (Withdrawn) The protein profiling method of claim 22, wherein the second target antigen is  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, uiduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-actvator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

28. (Withdrawn) The protein profiling method of claim 22, wherein the second target antigen is an indicator of cell number, organelle number, cell size, organelle size, cell volume, or organelle volume.
29. (Withdrawn) The protein profiling method of claim 22, wherein the second target antigen comprise LAMP-1, LAMP-2, saposin C, CD45 leukocyte common antigen, LIMP II, CD63.
30. (Withdrawn) The protein profiling method of claim 22, wherein the microsphere has a diameter of about 5  $\mu\text{m}$ .
31. (Withdrawn) The protein profiling method claim 22, wherein the LSD is Fabry; Mucopolysaccharidosis type I ("MPS I"); Mucopolysaccharidosis type II ("MPS-II"); Mucopolysaccharidosis type III ("MPS-III"); Mucopolysaccharidosis type IV ("MPS-IV"); or Glycogen storage disease II ("Pompe").
32. (Withdrawn) The protein profiling method claim 22, wherein the LSD is Gaucher disease types I / II / III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB; Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IIID; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis; Fucosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ -Mannosidosis; Mucolipidosis type I; Mucolipidosis types II / III;

Mucopolipidosis type IIIC; Mucopolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid Lipofuscinosis, CLN3; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pycnodysostosis; or Sialic acid storage disease.

33. (Withdrawn) A protein profiling method of screening for lysosomal storage disorder (“LSD”) in a target biological sample comprising:

- a) determining a target quantity of a target biomolecule from the target biological sample of a target animal;
- b) determining a cell quantity of a cell marker from the target biological sample of a target animal;
- c) assigning an adjusted target quantity to the target biomolecule by calculating a target proportion between the target quantity of the target biomolecule and the cell quantity of the cell marker;
- d) obtaining a reference quantity of a reference biomolecule from the reference biological sample of a reference animal;
- e) obtaining a cell quantity of a cell marker from the reference biological sample of a reference animal;
- f) assigning an adjusted reference quantity to the reference biomolecule by calculating a reference proportion between the reference quantity of the reference biomolecule and the cell quantity of the cell marker;

- g) comparing the adjusted target quantity to an adjusted reference quantity;
- wherein,
- the target biomolecule comprises a LSD associated biomolecule; and
- the target biomolecule is the same or equivalent to a reference biomolecule;
- the cell marker is the same or equivalent to a cell marker reference;
- a deviation of the adjusted target quantity from the adjusted reference quantity is a pre-clinical or clinical indication of a specific LSD.
- the target quantity of the target biomolecule comprises an amount or activity level of the target biomolecule.
- the cell quantity of the target biomolecule comprises an amount or activity level of the cell marker;
- the cell marker being an indicator of cell number, organelle number, cell size, organelle size, cell volume, or organelle volume.

34. (Withdrawn) The protein profiling method of claim 33, wherein the target biological sample is selected from a cellular extract, blood, plasma, or urine.

35. (Withdrawn) The protein profiling method of claim 33, wherein the target biomolecule is  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, or saposin C.

36. (Withdrawn) The protein profiling method of claim 33, wherein the target biomolecule is  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, Iduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -

N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase, N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2-activator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

37. (Withdrawn) The protein profiling method of claim 33, wherein the cell marker comprises a protein indicator of cell number, organelle number, cell size, organelle size, cell volume, or organelle volume.

38. (Withdrawn) The protein profiling method of claim 33, wherein the cell marker comprises: LAMP-1, LAMP-2, saposin C, CD45 leukocyte common antigen, LIMP II, CD63.

39. (Withdrawn) The protein profiling method of claim 33, wherein the target biomolecule or cell marker comprises an intracellular biomolecule.

40. (Withdrawn) The protein profiling method of claim 33, wherein the LSD is Fabry; Mucopolysaccharidosis type I ("MPS I"); Mucopolysaccharidosis type II ("MPS-II"); Mucopolysaccharidosis type III ("MPS-III"); Mucopolysaccharidosis type IV ("MPS-IV"); or Glycogen storage disease II ("Pompe").

41. (Withdrawn) The protein profiling method of claim 33, wherein the LSD is Gaucher disease types I / II / III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB;

Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IVB; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick. disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis; Fucosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ -Mannosidosis; Mucolipidosis type. I; Mucolipidosis types II/ III; Mucolipidosis type IIIC; Mucolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid Lipofuscinosis, CLN3; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pycnodysostosis; or Sialic acid storage disease.

42. (Currently Amended) A protein profiling method of detecting multiple Lysosomal Storage Disease (“LSD”) target antigens in a dried blood or plasma sample, the protein profiling method comprising:

- (a) determining a target ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or and~~ and  $\alpha$ -glucosidase from a target biological dried blood or plasma sample ~~of the target animal of a human subject~~ subject;
- (b) determining a target quantity of either LAMP-1 or saposin C from the target biological dried blood or plasma sample ~~of the target animal of the human subject~~ of the human subject;
- (c) assigning ~~an adjusted target quantity~~ a set of adjusted target quantities by calculating a set of target ~~proportion~~ proportions between the target ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or and~~ and  $\alpha$ -glucosidase and the target quantity of either LAMP-1 or saposin C;
- (d) obtaining a reference ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or and~~ and  $\alpha$ -glucosidase from a reference biological dried blood or plasma sample from a reference ~~animal~~ human

- subject, or group of reference ~~animals~~ human subjects, having a known LSD pre-clinical or clinical status;
- (e) obtaining a reference quantity of either LAMP-1 or saposin C from the reference biological dried blood or plasma sample from ~~a animal~~ the reference human subject, or group of reference ~~animals~~ human subjects, having a known LSD pre-clinical or clinical status;
- (f) assigning ~~an adjusted reference quantity~~ a set of adjusted reference quantities by calculating a set of reference ~~proportion~~ proportions between the reference ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or~~ and  $\alpha$ -glucosidase and the reference quantity of either LAMP-1 or saposin C; and
- (g) determining a deviation of the set of adjusted target ~~quantity~~ quantities compared to the set of adjusted reference ~~quantity~~ quantities; and  
wherein:  
the determination of the target ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or~~ and  $\alpha$ -glucosidase, the reference ~~quantity~~ quantities of  $\alpha$ -iduronidase ~~or~~ and  $\alpha$ -glucosidase, the target ~~quantity~~ quantities of either LAMP-1 or saposin C, and the reference ~~quantity~~ quantities of either LAMP-1 or saposin C, are performed using a capture antibody conjugated to a microsphere, the microsphere having at least a first fluorophore and a second fluorophore, wherein the capture antibody is capable of binding to  $\alpha$ -iduronidase or  $\alpha$ -glucosidase or LAMP-1 or saposin C;  
and a significant deviation of any of the adjusted target ~~quantity~~ quantities compared to the adjusted reference ~~quantity~~ quantities is a pre-clinical or clinical indication of a specific LSD, wherein a deviation is significant if the absolute value of the deviation is greater than or equal to a standard deviation calculated by a Mann-Whitney *U* (MWU) test.

43. (Cancelled)

44. (Cancelled)



45. (Cancelled)

46. (Currently Amended) The protein profiling method of claim 42, wherein the sample is selected from ~~a cellular extract, dried blood, or plasma, or urine.~~ dried blood, or plasma, or urine.

47. (Cancelled)

48. (Cancelled)

49. (Cancelled)

50. (Cancelled)

51. (Original) The protein profiling method of claim. 42, wherein the microsphere has a diameter of about 5 $\mu$ m.

52. (Previously Amended) The protein profiling method of claim 42, wherein the first fluorophore and the second fluorophore exhibit distinct characteristic fluorescence emission classification parameters.

53. (Previously Amended) The protein profiling method of claim 42 wherein the first fluorophore and the second fluorophore differ in an intensity of at least one fluorescence emission classification parameter.

54. (Cancelled)

55. (Cancelled)

56. (Original) The protein profiling method of claim 42, wherein the LSD is Fabry; Mucopolysaccharidosis type I (“MPS I”); Mucopolysaccharidosis type II (“MPS-II”);

Mucopolysaccharidosis type III (“MPS-III”); Mucopolysaccharidosis type IV (“MPS-IV”);  
or Glycogen storage disease II (“Pompe”).

57. (Original) The protein profiling method of claim 42, wherein the LSD is Gaucher disease types I / II/ III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB; Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IIID; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis; Fucosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ -Mannosidosis; Mucolipidosis type I; Mucolipidosis types II / III; Mucolipidosis type. IIIC; Mucolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1 ; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid Lipofuscinosis, CLN3; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pycnodysostosis; or Sialic acid storage disease.

58. (Withdrawn) A protein profiling method of screening for lysosomal storage disorder (“LSD”) in a target biological sample, the protein profiling method comprising:

- a) exposing a pooled population of target capture microspheres to the target biological sample, the target capture microspheres having distinct subsets, and each distinct subset having: (i) one or more characteristic classification parameters that

distinguishes one target capture microsphere of one subset from those of another target capture microsphere subset according to a predetermined discriminate microsphere function table; and (ii) a distinct capture antibody that can bind a specific subset of LSD antigens;

- b) adding a pooled population of detection antibodies to the exposed pooled population of the target capture microspheres, the pooled population of target detection antibodies having distinct subsets that correspond to and bind to the same specific subset of LSD antigens coupled to each distinct subset of the target capture microspheres, forming an exposed pooled population of target capture microsphere complexes having distinct subsets;
- c) passing the an exposed pooled population of target capture microsphere complexes having distinct subsets through an examination zone;
- d) determining the identity and quantity of each specific subset of LSD target antigen of interest, if present, in the sample by (i) collecting data relating to one or more subsets of target capture microsphere classification parameters that distinguishes one target capture antibody microsphere of one subset from those of another target capture antibody microsphere subset according to a predetermined discriminate function table, including the fluorescence emission intensities, (ii) collecting data relating to the presence or absence of a corresponding detection antibody that binds the subset of specific LSD antigen, (iii) quantifying each corresponding detection antibody on each subset of capture antibody microsphere; and

- e) comparing the identity and quantity of each specific subset of LSD target antigen of interest from the sample obtained from a patient having an unknown LSD clinical status to the identity and quantity of the same specific subset of LSD target antigen of interest from the sample obtained from a patient having a known LSD clinical status.

59. (Withdrawn) The protein profiling method of claim 58, wherein the sample is selected from a cellular extract, blood, plasma, or urine.

60. (Withdrawn) The protein profiling method of claim 58, wherein the specific subset of LSD antigens is  $\alpha$ -iduronidase,  $\alpha$ -glucosidase, or saposin C.

61. (Withdrawn) The protein proofing method of claim 58, wherein the specific subset of LSD antigens is  $\beta$ -glucosidase,  $\alpha$ -galactosidase A, Iduronate-2-sulphatase,  $\alpha$ -iduronidase, N-acetylgalactosamine 4-sulphatase, galactose 6-sulphatase, acid sphingomyelinase, galactocerebrosidase, arylsulphatase A, saposin B, heparan-N-sulphatase,  $\alpha$ -N-acetylglucosaminidase, acetylCoA: glucosamine N-acetyltransferase N-acetylglucosamine 6-sulphatase,  $\beta$ -galactosidase,  $\beta$ -glucuronidase, aspartylglucosaminidase, acid lipase,  $\beta$ -hexosaminidase A,  $\beta$ -hexosaminidase B, GM2- activator, acid ceramidase,  $\alpha$ -L-fucosidase,  $\alpha$ -D-mannosidase,  $\beta$ -D-mannosidase, neuraminidase, phosphotransferase, phosphotransferase g-subunit, palmitoyl protein thioesterase, tripeptidyl peptidase I, cathepsin K,  $\alpha$ -galactosidase B, or sialic acid transporter.

62. (Withdrawn) The protein profiling method of claim 58, wherein the specific subset of LSD antigens comprise an indicator of cell number, organelle number, cell size, organelle size, cell volume, or organelle volume.
63. (Withdrawn) The protein profiling method of claim 62, wherein the specific subset of LSD antigens comprise LAMP-1, LAMP-2, saposin C, CD45 leukocyte common antigen, LIMP TT, CD63.
64. (Withdrawn) The protein profiling method of claim 58, wherein the microsphere has a diameter of about 5 $\mu$ m.
65. (Withdrawn) The protein profiling method of claim 58, wherein the target capture microspheres in each distinct subset exhibit two or more characteristic fluorescence emission classification parameters.
66. (Withdrawn) The protein profiling method of claim 58 wherein the target capture microspheres of one subset differ from the target capture microspheres of another subset in an intensity of at least one fluorescence emission classification parameter.
67. (Withdrawn) The protein profiling method of claim 58, wherein each subset of target detection antibodies is conjugated to a fluorescent detection label.
68. (Withdrawn) The protein profiling method of claim 58, wherein the quantity of each specific subset of LSD target antigen of interest is proportional another specific subset of LSD target antigen of interest.

69. (Withdrawn) The protein profiling method of claim 58, wherein results of said protein profiling method are displayed in real time.
70. (Withdrawn) The protein profiling method of claim 58, wherein the LSD is Fabry; Mucopolysaccharidosis type I (“MPS I”); Mucopolysaccharidosis type II (“MPS-II”); Mucopolysaccharidosis type III (“MPS-III”); Mucopolysaccharidosis type IV (“MPS-IV”); or Glycogen storage disease II (“Pompe”).
71. (Withdrawn) The protein profiling method of claim 58, wherein the LSD is Gaucher disease types I / II / III; Cystinosis; Mucopolysaccharidosis type VI; Mucopolysaccharidosis type IVA; Niemann-Pick disease types A/B; Metachromatic leucodystrophy; Metachromatic leucodystrophy; Mucopolysaccharidosis type IIIA; Mucopolysaccharidosis type IIIB; Mucopolysaccharidosis type IIIC; Mucopolysaccharidosis type IIID; Mucopolysaccharidosis type VII; Mucopolysaccharidosis type IVB; Niemann-Pick disease type C1; Niemann-Pick disease type C2; Cholesterol ester storage disease; Aspartylglucosaminuria; GM1-Gangliosidosis types I/II/III; GM2-Gangliosidosis type I; GM2-Gangliosidosis type II; GM2-Gangliosidosis; Farber Lipogranulomatosis; Fucosidosis; Galactosialidosis types I / II;  $\alpha$ -Mannosidosis types I / II;  $\beta$ -Mannosidosis; Mucolipidosis type I; Mucolipidosis types II / III; Mucolipidosis type IIIC; Mucolipidosis type IV; Multiple sulphatase deficiency; Neuronal Ceroid Lipofuscinosis, CLN1; Neuronal Ceroid Lipofuscinosis, CLN2; Neuronal Ceroid Lipofuscinosis, CLN3; Neuronal Ceroid Lipofuscinosis, CLN5; Neuronal Ceroid Lipofuscinosis, CLN8; Pseudotumor cerebri; or Sialic acid storage disease.

72. (Withdrawn) A composition used for diagnosing a lysosomal storage disorder (“LSD”) comprising:

a first microsphere conjugated to a first capture antibody capable of binding  $\alpha$ -iduronidase;

a second microsphere conjugated to a second capture antibody capable of binding  $\alpha$ -glucosidase;

a third microsphere conjugated to a third capture antibody capable of binding saposin C; a fourth microsphere conjugated to a fourth capture antibody capable of binding LAMP-1;

a first detection antibody conjugated to a fluorescent detection label and capable of binding  $\alpha$ -iduronidase;

a second detection antibody conjugated to a fluorescent detection label and capable of binding  $\alpha$ -glucosidase;

a third detection antibody conjugated to a fluorescent detection label and capable of binding saposin C;

a second detection antibody conjugated to a fluorescent detection label and capable of binding LAMP-1;

wherein,

the first microsphere, the second microsphere, the third microsphere and the fourth microsphere contain a specific ratio of fluorophores and are spectrally distinct from each other; the first microsphere, the second microsphere, the third microsphere and the fourth microsphere have a diameter of about 5  $\mu$ m; and the LSD is Fabry;

Mucopolysaccharidosis type I (“MPS I”); Mucopolysaccharidosis type II (“MPS-II”); Mucopolysaccharidosis type IV (“MPS-III”); Mucopolysaccharidosis type IV (“MPS-IV”); or Glycogen storage disease II (“Pompe”).

73. (Withdrawn) A protein profiling method of screening for lysosomal storage disorder (“LSD”) in a target biological sample, the protein profiling method comprising:

- a) exposing a pooled population of target capture microspheres to the target biological sample, the target capture microspheres having distinct subsets, and each distinct subset having: (i) one or more characteristic classification parameters that distinguishes one target capture microsphere of one subset from those of another target capture microsphere subset according to a predetermined discriminate microsphere function table; and (ii) a distinct capture antibody that can bind a specific subset of LSD antigens; wherein, the pooled population of target capture microspheres comprises: a first microsphere conjugated to a first capture antibody capable of binding  $\alpha$ -iduronidase; a second microsphere conjugated to a second capture antibody capable of binding  $\alpha$ -glucosidase; a third microsphere conjugated to a third capture antibody capable of binding saposin C; a fourth microsphere conjugated to a fourth capture antibody capable of binding LAMP-1;
- b) adding a pooled population of detection antibodies to the exposed pooled population of the target capture microspheres, the pooled population of target detection antibodies having distinct subsets that correspond to and bind to the same specific subset of LSD antigens coupled to each distinct subset of the target capture microspheres, forming an exposed pooled population of target capture microsphere



complexes having distinct subsets, wherein the pooled population of detection antibodies comprises: a first detection antibody conjugated to a fluorescent detection label and capable of binding  $\alpha$ -iduronidase; a second detection antibody conjugated to a fluorescent detection label and capable of binding  $\alpha$ -glucosidase; a third detection antibody conjugated to a fluorescent detection label and capable of binding saposin C; a second detection antibody conjugated to a fluorescent detection label and capable of binding LAMP-1;

- c) passing the an exposed pooled population of target capture microsphere complexes having distinct subsets through an examination zone;
- d) determining the identity and quantity of each specific subset of LSD target antigen of interest, if present, in the sample by (i) collecting fluorescent data relating to one or more subsets of target capture microsphere classification parameters that distinguishes one target capture antibody microsphere of one subset from those of another target capture antibody microsphere subset according to a predetermined discriminate function table, including the fluorescence emission intensities, (ii) collecting data relating to the presence or absence of a corresponding detection antibody that binds the subset of specific LSD antigen, (iii) quantifying each corresponding detection antibody on each subset of capture antibody microsphere; and
- e) comparing the identity and quantity of each specific subset of LSD target antigen of interest from the sample obtained from a patient having an unknown LSD clinical

status to the identity and quantity of the same specific subset of LSD target antigen of interest from the sample obtained from a patient having a known LSD clinical status;

wherein; the LSD is Fabry; Mucopolysaccharidosis type I (“MPS I”); Mucopolysaccharidosis type II (“MPS-II”); Mucopolysaccharidosis type III (“MCPS-III”); Mucopolysaccharidosis type IV (“MPS-IV”); or Glycogen storage disease II (“Pompe”); the sample is selected from a cellular extract, blood, plasma, or urine, the microspheres have a diameter of about 5 $\mu$ m; the target capture microspheres of one subset differ from the target capture microspheres of another subset in an intensity of at least one fluorescence emission classification parameter; the quantity of each specific subset of LSD target antigen of interest is proportional another specific subset of LSD target antigen of interest; and the results of said protein profiling method are displayed in real time.

74. (New) A protein profiling method of detecting multiple Lysosomal Storage Disease (“LSD”)

target antigens in a dried blood or plasma sample, the protein profiling method comprising:

- (a) determining a target quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase from a target biological dried blood or plasma sample of a human subject;
- (b) determining a target quantity of LAMP-1 from the target biological dried blood or plasma sample of the human subject;
- (c) assigning a set of adjusted target quantities by calculating a set of target proportions between the target quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase and the target quantity of LAMP-1;
- (d) obtaining reference quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase from a reference biological dried blood or plasma sample from a reference human subject, or group of

- reference human subjects, having a known LSD pre-clinical or clinical status;
- (e) obtaining a reference quantity of LAMP-1 from the reference biological dried blood or plasma sample from the reference human subject, or group of reference human subjects, having a known LSD pre-clinical or clinical status;
  - (f) assigning a set of adjusted reference quantities by calculating a set of reference proportions between the reference quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase and the reference quantity of LAMP-1; and
  - (g) determining a deviation of the set of adjusted target quantities compared to the set of adjusted reference quantities;

wherein;

the determination of the target quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase, the reference quantities of  $\alpha$ -iduronidase and  $\alpha$ -glucosidase, the target quantities of LAMP-1, and the reference quantities of LAMP-1, are performed using an immunoassay;

wherein the immunoassay is performed using a capture antibody conjugated to a microsphere, the microsphere having at least a first fluorophore,

wherein the immunoassay further comprises a detection antibody conjugated to a detection molecule;

wherein the capture antibody and the detection antibody are each capable of binding to  $\alpha$ -iduronidase or  $\alpha$ -glucosidase or LAMP-1 or saposin C; and

wherein a significant deviation of any of the adjusted target quantities compared to the adjusted reference quantities is a pre-clinical or clinical indication of a specific LSD, wherein a deviation is significant if the absolute value of the deviation is greater than or equal to a standard deviation calculated by a Mann-Whitney *U* (MWU) test.